Regulation of KIF23 by miR-107 controls replicative tumor cell fitness in mouse and human hepatocellular carcinoma

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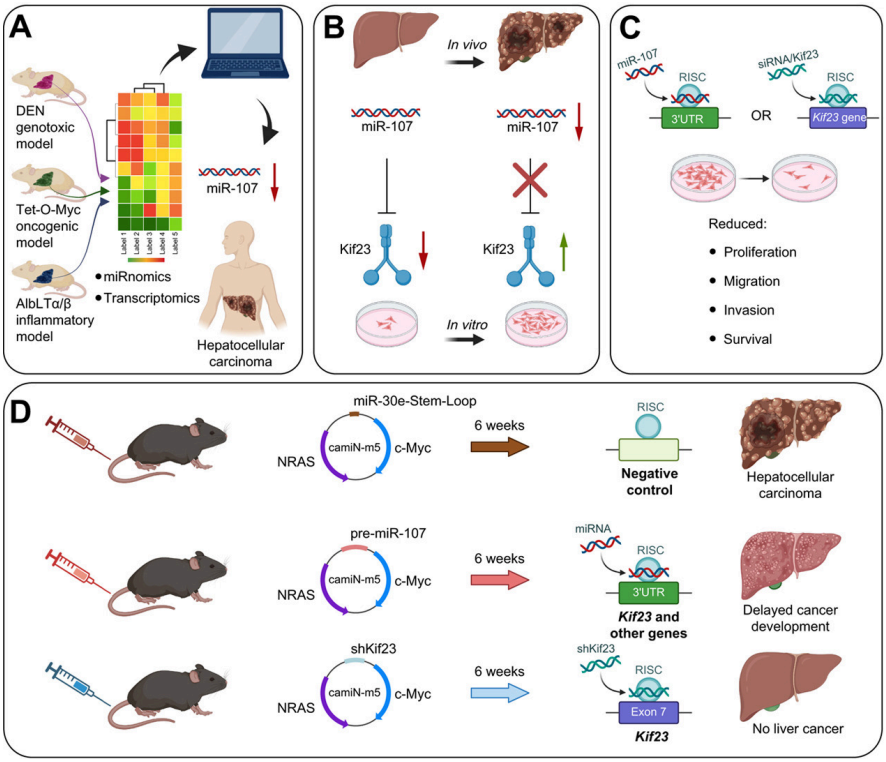
PUBLIZIERT AM
2025-03-01

JOURNAL
Journal of Hepatology

LINK
https://doi.org/10.1016/j.jhep.2024.08.025

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Abstract

Background & aims: In hepatocellular carcinoma (HCC), successful translation of experimental targets identified in mouse models to human patients has proven challenging. In this study, we used a comprehensive transcriptomic approach in mice to identify novel potential targets for therapeutic intervention in humans.

Methods: We analyzed combined genome-wide miRNA and mRNA expression data in three pathogenically distinct mouse models of liver cancer. Effects of target genes on hepatoma cell fitness were evaluated by proliferation, survival and motility assays. TCGA and GEO databases, in combination with tissue microarrays, were used to validate the mouse targets and their impact on human HCC prognosis. Finally, the functional effects of the identified targets on tumorigenesis and tumor therapy were tested in hydrodynamic tail vein injection-based preclinical HCC models in vivo.

Results: The expression of miR-107 was found to be significantly reduced in mouse models of liver tumors of various etiologies and in cohorts of humans with HCC. Overexpression of miR-107 or inhibition of its novel target kinesin family member 23 (Kif23) significantly reduced proliferation by interfering with cytokinesis, thereby controlling survival and motility of mouse and human hepatoma cells. In humans, KIF23 expression was found to be a prognostic marker in liver cancer, with high expression associated with poor prognosis. Hydrodynamic tail vein injection of vectors carrying either pre-miR-107 or anti-Kif23 shRNA inhibited the development of highly aggressive c-Myc-NRAS-induced liver cancers in mice.

Conclusions: Disruption of the miR-107/Kif23 axis inhibited hepatoma cell proliferation in vitro and prevented oncogene-induced liver cancer development in vivo, offering a novel potential avenue for the treatment of HCC in humans.

Impact and implications: Our study revealed the central role of the miR-107/KIF23 axis in controlling tumor cell fitness and hepatocellular carcinoma progression. The results demonstrate that the overexpression of miR-107 or silencing of its target, KIF23, markedly suppresses the proliferation, survival, and motility of human and mouse hepatoma cells. In this work, we demonstrate that the disruption of miR-107/Kif23 signaling effectively protects mice from an aggressive form of oncogene-induced liver cancer in vivo, implying that targeting miR-107/KIF23 might be a novel therapeutic approach for hepatocellular carcinoma in humans.